UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/893,615	06/29/2001	Gerald W. Fischer	07787.0041-01	5776

22852 7590 06/15/2004

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
1300 I STREET, NW
WASHINGTON, DC 20005

EXAMINER	
PORTNER, VIRGINIA ALLEN	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 06/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/893,615	FISCHER ET AL.	
	Examiner	Art Unit	
	Ginny Portner	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *32,34,36,37,39 and 41-44* is/are pending in the application.

4a) Of the above claim(s) *41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *32,34,36,37,39 and 42-44* is/are rejected.

7)☐ Claim(s) *34,36* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/5/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 32,34,36,37,39,42-44 are under consideration.
Claim 41 stands withdrawn from consideration.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 5, 2004 has been entered.

Objections/Rejections Withdrawn

2. The sequence letter and objection to the Brief Description of the Drawings has been obviated by amendment of the Specification.

3. Claim 32 is no longer rejected under the judicially created doctrine of obviousness type double patenting, over claims 1-6 of US Patent 5,955,074, in light of the claims to recite "monoclonal chimeric or humanized antibody".

4. All prior art rejections are herein withdrawn in light of the newly submitted combination of claim limitations.

Objections/Rejections Maintained

5. Claims 32,34,36-37,39,42-44 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment and prevention of infection caused by Gram positive bacteria with a polyclonal antibody to Gram positive lipoteichoic acid obtained from Staphylococcus, or with a monoclonal antibody MAB96-110, does not reasonably provide

enablement for the utilization of any monoclonal, fragment, region or derivative of an antibody that binds to any portion of a lipoteichoic acid, SEQ ID NO 1 or 2 or is a derivative of SEQ ID NO 88 or 89, for the treatment or prevention of Gram positive bacterial infection. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims, is maintained for reasons of record in paper numbers 14 and 18.

Response to Arguments

6. Applicant's arguments filed April 5, 2004 have been fully considered but they are not persuasive.

7. The rejection of claims 32,34,36-37,39,42-44 rejected under 35 U.S.C. 112, first paragraph (scope of enablement) is traversed on the grounds that:

a. "The Fc fragment does not participate in epitope binding and therefore need not be enabled by the specification"

8. It is the position of the examiner that claims do encompass the administration of any derivative portion of a monoclonal antibody through the recitation of "a fragment, region or derivative of the monoclonal antibody". The Fc fragment would bind to a cell surface receptor that comprises epitopes, and therefore would bind to an epitope, though not through a CDR region or variable region of the antibody.

9. Additionally, the claims now only require the administration of a composition that comprises a "pharmaceutically acceptable carrier" through claiming the invention by the phrase "at least one of" A, and B and C, wherein the C component is a "pharmaceutically acceptable

carrier". Applicant's arguments are not commensurate in scope with the instantly amended claims.

10. Applicant asserts that "But for regions, fragments, derivatives of an antibody that do not bind to LTA, the specification does not enable these antibody forms for treating or preventing Gram positive bacterial infections".

11. The examiner agrees with Applicant's statement, and views this statement as one that is in support of the scope of enablement rejection made of record. The fragment, region or derivative of the chimeric or humanized monoclonal are not defined in the claims to evidence any specific type of binding as required by the chimeric or humanized antibody.

12. Additionally, claims 34,36, 37,39, 42-44 while requiring some of the recited species to bind to SEQ ID NO 1, or 2 or to evidence the coding sequence of the antibody defined by Figure 12, or a homolog of the sequence of Figure 12, the antibodies that bind to a specific amino acid sequence would not evidence binding for Lipoteichoic acid, as Lipoteichoic acid is not a peptide molecule (see definitions provided above).

13. A SWISS-PROT data base search for sequences with at least 70% sequence identity to any portion of SEQ ID NO 1 or 2, resulted in detecting a sequence that is an ABC transporter, membrane spanning protein from the bacterium Agrobacterium tumefaciens (see sequence alignment attached hereto which shows 90% identity of a region of 10 amino acids); the overall size of the ABC transmembrane protein is about 802 amino acids. Additionally, a shared amino acid sequence that showed 59% sequence identity over the 22 amino acids of SEQ ID NO 2, or 90% sequence identity over a fragment of Seq ID NO 2 (RIPLQL_AAG) , the sequence being

embedded in a larger sequence of 361 amino acids in an Archaeoglobus fuligidus transmembrane protein (see sequence alignment provided); SEQ ID NO 1 and 2 show some sequence homology with bacterial transport protein molecules and not lipoteichoic acids.

14. Therefore, claims 34,36, 37,39, 42-44 are not enabled for binding to lipoteichoic acids through administration of a peptide binding antibody that will bind to a transmembrane protein homolog, or any peptide homolog, because the claims require the antibody to bind to a lipoteichoic acid molecule.

15. While the claims were previously drawn to the administration of any type antibody that comprised anti-lipoteichoic antibodies, the instantly amended claims are directed to the administration of a monoclonal antibody that binds to an epitope of lipoteichoic acid (independent claims 32, 42 and 43), or a peptide amino acid sequence and not lipoteichoic acid (independent claim 37). From the instant specification, the monoclonal antibody MAB 96-110, was obtained through administration of a whole cell antigen, and not isolated lipoteichoic acid that was free of any contaminating protein molecules, therefore, monoclonal antibody MAB 96-110, while obtained through immunization with an antigen that comprised or was associated with lipoteichoic acid, does not bind to lipoteichoic acid, but to a peptide.

16. With respect to the cited references in the scope of enablement rejection used to show unpredictability of an anti-lipoteichoic antibody to treat or prevent disease/infection, Applicant asserts that "these references are irrelevant to whether the claimed invention is enabled", and asserts that any negative side effects associated with administration of an antibody is the responsibility of the Food and Drug Administration, and not the USPTO.

17. While the examiner agrees that the USPTO is not the Food and Drug Administration, the scope of enablement rejection needs to address the Forman Factors which includes predictability in the art.

The Forman Factor analysis for the instantly claimed invention is as follows:

1) the quantity of experimentation necessary: undue, due to the breath of the claims directed to any gram positive bacterial lipoteichoic acid binding monoclonal antibody, or the monoclonal binding to any epitope or homolog of the recited peptide containing epitope, to provide protection to any subject against any gram positive bacterial infection in light of evidence provided that all anti-lipoteichoic acid antibodies are not protective antibodies and would not serve to treat or prevent infection caused by any gram positive bacteria.

2)the amount of direction and guidance presented; guidance specific for specific polyclonal and monoclonal antibodies, but not enabled over the full scope of the instantly claimed methods; especially for DNA sequences for antibodies that only share 70% sequence homology with the sequence of Figure 12 as these sequences have not been described with structure correlated with the function to provide protection against infection caused by any gram positive bacterial pathogen.

3)the presence or absence of working examples: working examples relative to what is now claimed: a single species Mab 96-110 or Hu 96-110 that binds to two peptides does not enable the full scope of any monoclonal derivative, fragment, region or homolog to provide protection when treating or preventing infection caused by any gram positive bacteria.

4)the nature of the invention: immunotherapy is well known in the art; the ability of monoclonals to any epitope of any lipoteichoic acid molecule obtained from Staphylococcus

epidermidis to provide protection against infection caused by any gram positive bacteria is not well known in the art.

5)the state of the prior art: unpredictable with respect to the ability of an anti-lipoteichoic antibody being protective in a method of treating or preventing infection caused by any gram positive bacteria;

6)the relative skill of those in the art: high with respect to producing antibodies

7) **the predictability or unpredictability of the art:** The examiner cited published journal references to provide evidence of unpredictability of anti-lipoteichoic acid antibodies being protective to treat or prevent infection; and

8)the breadth of the claims: broad but clear with respect to the recited methods step of administering, but not clear with respect to what is being administered (see objection and rejection under 35 USC 112, second paragraph rejections below).

18. The instantly claimed methods are only enabled for the administration of humanized or monoclonal antibodies of MAB-96-110 (also known as HU 96-110) in a method of treating or preventing gram-positive bacterial infection and not the full scope of the instantly claimed invention. The scope of enablement is maintained for reasons of record, and arguments set forth above.

Information Disclosure Statement

19. The information disclosure statement filed April 5, 2004 has been considered.

Double Patenting

20. Claims 32,37, 42, 43 of this application conflict with claims 27-30 of Application No. **10/323,926**. 37 CFR 1.78(b) provides that when two or more applications filed by the same

applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

21. Claims 32,37, 42, 43 of this application conflict with claims 27-30 of Application No. **10/323,927**. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

22. Claims 32, 37, 42, 43 of this application conflict with claims 14-15, 24-25 of Application No. **10/601,171**. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

Claim Objections

23. Claims 34 and 36 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

24. Claims 34 and 36 depend from claim 32, wherein the binding specificity of the recited monoclonal Hu96-110 is defined to be a specific amino acid sequence of SEQ ID NO 1 or 2, but the monoclonal antibody of claim 32 is directed to lipoteichoic acid, and not an amino acid containing molecule, therefore in light of the definition of lipoteichoic acid, claims 34 and 36 broaden the scope of claim 32 that requires the monoclonal antibody to bind to lipoteichoic acid,

and not proteins associated with lipoteichoic acid as recited in claims 34 and 36. What is now claimed in claims 34and 36 is the administration of a monoclonal antibody specific for an amino acid sequence not a monoclonal antibody that binds to lipoteichoic acid from a gram –positive bacteria.

Lipoteichoic acid by definition is :

25. teichoic acid: bacterial polysaccharide that is rich in phophodiester linkages (On-line Medical Dictionary); and are one of two classes of polymers constituting the cell walls of Gram-positive bacteria, but also found intracellularly; linear polymers of polyol (ribitol phosphate or glycerol phosphate) carrying **d-alanyl** residues esterified to OH groups and glycosidically linked sugars (Stedman's medical dictionary); and lipoteichoic acid: compounds are formed from teichoic acid linked to glycolipid and found in the walls of most gram positive bacteria (On-line Medical Dictionary). The amino acid sequences recited in the claims are peptide sequences, and not a lipoteichoic acid molecule.

26. WO96/23896 shows a structural drawing of lipoteichoic acid on the front of the document; this molecule does not contain any peptide amino acid sequences.

Claim Rejections - 35 USC § 112

27. Claims 32, 34, 36, 37, 39, 42-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 32 and 37 have been amended to recite the phrase:

> "at least one of **a** monoclonal chimeric or humanized antibody to lipoteichoic acid of gram positive bacteria **and** a fragment, region or derivative of the monoclonal chimeric or humanized antibody **and** a pharmaceutically acceptable carrier".

The invention, as amended, includes the administering of a pharmaceutically acceptable carrier without an antibody for the treating or preventing gram-positive infection in light of the newly

submitted combination of claim limitations. The invention is not clearly, nor distinctly claimed through administering a pharmaceutical composition that only comprises a pharmaceutically acceptable carrier.

Claims 34, 36-37, 39, 42 and 43 all recite a combination of claim limitations that are intended to define an anti-lipoteichoic acid monoclonal antibody, but recite amino acid sequences or DNA molecules that encode an antibody that binds to a peptide (MAB 96-110 binds of SEQ ID NO 1 or 2), and not a lipoteichoic acid epitope/molecule; the claims do not recite a combination of claim limitations that are internally consistent with the art recognized definitions for lipoteichoic acid and peptides. Lipoteichoic acids and peptides are molecules that are structurally distinct from each other. The claims which recite a monoclonal antibody that binds a peptide, or an antibody that is defined in the instant specification to bind a peptide but is functionally defined to bind to a lipid portion or teichoic acid portion of a lipoteichoic acid do not distinctly claim Applicant's invention.

Claim Rejections - 35 USC § 102

Please Note: The instantly claimed invention is being read to include within its scope, the administration of monoclonal antibodies, a type of derivative of a humanized or chimeric monoclonal antibody, as well as chimeric and humanized antibodies that react with gram positive bacteria, as well as other pathogens (such as gram negative bacteria and fungi).

28. Claim 32 is rejected under 35 U.S.C. 102(b) as being anticipated by Gazmuri et al (1991, New England Journal of Medicine, in light of the letters to the editor that follow the article, especially on page 281, col. 1, paragraph 1).

Gazmuri et al disclose a humanized monoclonal antibodies designated Ha-1a that is secreted by a mouse-human heteromyeloma cell, that antibody evidencing binding for gram negative bacteria, as well as gram positive bacteria (see last paragraph of document), the method comprising the step of : administering to the patient (rabbit or mice) an effective amount of a pharmaceutical composition (hybridoma fluid containing HA-1A which was protective) and binds to surface associated lipid (see last paragraph of document).

The methods step of the prior art, and the methods step of instantly claimed invention which is "administering" to a patient without gram positive bacterial infection (preventing or treating), is anticipated by Gazmuri et al, based upon the fact that the humanized antibody was found to also bind to gram positive bacteria lipid components (see page 281, col. 1, paragraph 1). The reference inherently anticipates the instantly claimed invention.

29. Claim 32 is rejected under 35 U.S.C. 102(e) as being anticipated by Fattom et al (US Pat. 5,770,208). Fattom et al disclose the instantly claimed invention, directed to a method of treating or preventing an infection caused by gram positive bacteria, specifically Staphylococcus aureus, wherein the method comprises the step of:

Administering a monoclonal antibody (a derivative of a humanized or chimeric antibody) to a patient, the antibody binding to lipoteichoic acid of a gram positive bacteria, wherein the monoclonal antibody of Fattom et al specifically binds to ß-hexosamine carbohydrate component associated with a gram positive bacterial teichoic acid antigen (discussion of the reference in paper number 18, paragraphs 39 and 40 are incorporated herein) and combined with a pharmaceutical carrier (see claims 18-23).

Additionally, the monoclonal antibodies of Fattom ('208) include: "[A]ntibodies can be whole immunoglobulin of any class, e.g., IgG, IgM, IgA, IgD, IgE, chimeric antibodies or hybrid antibodies with dual or multiple antigen or epitope specificities, or fragments (see '208, col.7, lines 21-36). Therefore the antibodies of Fattom are disclosed as monoclonal chimeric or humanized antibodies, (see all claims) and the method that comprises the step of :administering chimeric monoclonal antibodies to a patient to teach gram positive bacterial infection, specifically infection caused by Streptococcus aureus.

The reference anticipates the instantly claimed invention.

Conclusion

30. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.
31. Anderson (US Pat. 4,761,283) is cited to show immunogenic conjugates of capsular polymers.
32. Bucala et al (US Pat. 6,080,407) is cited to show a method that administers a humanized monoclonal antibody to prevent bacterial infection (see all claims).
33. Burnie et al (US PG-Pub Application 2003/0119101 A1 is cited to show the treatment of gram positive bacterial infection with inhibitors of ABC transport proteins, the inhibitors include antibodies (see [0030]).
34. Lee (US Pat. 6,365,156) is cited to show anti-peptidoglycan chimera in a method (claims 16-17 and 6, 11).
35. US Pat. 6,610,293 is cited to show chimeric or humanized anti-lipoteichoic antibodies directed to gram-positive bacteria.
36. US Pat. 4,888,279 is cited to show antibodies specific for d-alanyl-d-alanine of peptidoglycan are known in the art (see col. 5, lines 1-9).
37. Hook et al (PG-Pub 2002/0102262) is cited to show compositions of anti-Staphylococcus aureus antibodies for the prevention of infection (see all claims).
38. Hunter et al (US Pat. 4,744,982 and 4954449) are cited to show a recombinantly express anti-peptidoglycan human monoclonal antibody directed against the PRP of a gram-negative bacteria.
39. Richards (US Pat. 5,043,267) is cited to show monoclonal antibodies to both peptidoglycan and lipoteichoic acid (see detailed description test, paragraph (26) starting with the phrase: "The polyglycerolphosphate structural backbone").
40. Shockman et al (US Pat. 4,596,769) is cited to show anti-peptidoglycan monoclonal antibodies; US Pat. 4,596,769 defines peptidoglycan to contain "D" amino acids (see col. 3, lines 1-24).

41. Ulevitch et al (US Pat. 6,168,790 and PG-Pub 2003/0103969) are cited to show a monoclonal antibody that is able to block the effects of gram-positive bacterial infection (see all claims and entire document).

42. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (571) 272-0862. The examiner can normally be reached on 7:30-5:00 M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vgp
June 3, 2004

L. F. Smith

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600